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DIABETIC Medicine

STUDY PROTOCOLS

Producing a preference-based quality of LIFE measure to quantify the impact of HYPOGLYCAEMIA on people living with diabetes: A mixed-methods research protocol

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Abstract

Background: Assessment of patient-reported outcome measures (PROMs), including quality of life (QoL), is essential in diabetes research and care. However, a recent review concluded that current hypoglycaemia-specific PROMs have limited evidence of validity, reliability and responsiveness for assessing the impact of hypoglycaemia on QoL in people living with diabetes. None of the PROMs identified could be used directly to inform the cost-effectiveness of treatments and interventions. There is a need for a new hypoglycaemia-specific QoL PROM, which can be used directly to inform economic evaluations.

Aims: This project has three aims: (a) To develop draft PROM content for measuring the impact of hypoglycaemia on QoL in adults with diabetes. (b) To refine

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the draft content using cognitive debriefing interviews and psychometrics. This will result in a condition-specific PROM that can be used to quantify the impact of hypoglycaemia upon QoL. (c) To generate a preference-based measure (PBM) that will enable utility values to be calculated for economic evaluation.

Methods: A mixed-methods, three-stage design is used: (a) Qualitative interviews will inform the draft PROM content. (b) Cognitive debriefing interview data will be used to refine the draft PROM content. The PROM will be administered in a large-scale survey to enable psychometric validation. Final item selection for the PROM will be informed by psychometric performance, translatability assessment and input from stakeholder groups. (c) A classification system will be generated, comprising a reduced number of items from the PROM. A valuation survey will be conducted to derive a value set for the PBM.

KEYWORDS

diabetes, hypoglycaemia, patient-reported outcome measures, preference-based measure, psychometrics, qualitative research, quality of life

1 | INTRODUCTION

The global prevalence of diabetes is projected to rise to 783 million by 2045.[1] Diabetes management usually requires glucose-lowering medications, often with insulin or insulin secretagogues that have hypoglycaemia (low blood glucose) as a side-effect. Hypoglycaemia can have significant physiological and clinical consequences and affects the quality of life (QoL) of people living with diabetes (PLWD).[2]

QoL is a multidimensional construct, that encompasses three broad components: physical (e.g., pain, mobility), psychological (e.g., self-esteem, mood) and social (e.g., relationships with others).[3] Health-related quality of life (HRQoL) has been defined as "a term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life".[4] HRQoL measures can be generic (i.e., reflecting the impact of health or illness generally) or condition-specific (i.e., attributing QoL ratings to a particular medical condition or illness, or perhaps to a particular aspect of that condition).

A recent review of hypoglycaemia-specific patient-reported outcome measures (PROMs) found them limited in terms of their content and structural validity for assessing the impact of hypoglycaemia on QoL,[5] suggesting a new PROM is required. Assessments of QoL or HRQoL are increasingly incorporated in the economic evaluation of clinical interventions and regulatory decision-making; none of the PROMs evaluated in the review were suitable for this purpose, as they do not have the necessary scoring system based on preferences (i.e. are not preference-based measures, PBMs).[5] Whilst generic PBMs exist, they rarely reflect outcomes relevant (i.e., lack sensitivity) to the specific patient groups, and hence, over- or under-estimate the cost-effectiveness of the interventions examined.[6] Interventions that are designed to alleviate hypoglycaemia come at a financial cost to individuals or healthcare systems, and therefore it is important that they are evaluated appropriately in terms of cost-effectiveness analyses, which make use of valid and reliable PBMs, as well as their usefulness to the individual. Thus, there is a clear need for a new PROM and PBM to assess hypoglycaemia-specific HRQoL among PLWD, developed according to best-practice guidelines, with good validity and reliability, and able to directly inform the economic evaluation of health interventions.

Over the last decade, PBMs of health have been used increasingly in economic evaluation to inform health policy, including for submission to agencies such as the National Institute for Health and Care Excellence (NICE) in England.[7] A PBM consists of a classification system used to describe health, and an associated value set that generates a utility value for every health state defined by the classification system. PBMs are commonly combined with survival evidence to create quality-adjusted life years (QALYs). A QALY multiplies the value of health-related QoL, usually generated using a PBM, by the length of life to generate a single index that captures both mortality and morbidity of patients. The QALY can be used to provide a measure of the incremental benefits of an intervention, which can be compared to its incremental cost over a comparator. Interventions (e.g., for hypoglycaemia) can

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then be compared in terms of their incremental cost per QALY ratio.

As part of the Hypoglycaemia REdefining SOLutions for better liVEs (Hypo-RESOLVE) project (an international collaboration of clinicians, scientists, industry partners and PLWD[8]), the overall aim of this research is to develop a new valid and reliable PROM and associated PBM suitable for measuring the impact of hypoglycaemia on HRQoL in PLWD: Hypo-RESOLVE QoL.

2 | AIMS

This project has three aims:

1. To generate draft PROM content for measuring the impact of hypoglycaemia on HRQoL in PLWD based on deductive and inductive (qualitative interview) methods.
2. To refine the draft content using qualitative methods (cognitive debriefing interviews) and psychometric analyses. This will result in a condition-specific PROM that can be used to quantify the impact of hypoglycaemia upon HRQoL.
3. To generate a preference-based measure (PBM) from the PROM that will enable utility values to be generated each time the PROM is administered in order to derive QALYs.

3 | METHODS

3.1 | Project governance

The research has three governance groups who will be actively involved at key stages: the Scientific Group (comprising a diverse group of researchers including PROM developers, health economists, clinical academics and stakeholder representation from the Hypo-RESOLVE Consortium); the Advisory Group (comprising a diverse group of researchers and stakeholders with an interest in the project external to the Hypo-RESOLVE Consortium); and the Patient Advisory Committee (PAC) (comprising adults with type 1 or type 2 diabetes, and representatives from International Diabetes Foundation (IDF) and Juvenile Diabetes Research Foundation (JDRF)). PAC involvement will follow an existing framework to ensure that lived experience views are fully integrated into the PROM.[9]

To achieve the project aims, the research is split into three sequential stages (Figure 1). Stage 1 is complete. Stage 2 is ongoing (stage 2.1 is complete and stage 2.2 is ongoing), and stage 3 is planned.

3.1.1 | Stage 1 – Concept elicitation

The purpose of stage 1 is to generate draft content for the PROM (i.e., list of potential items, draft response options, draft instructions). Stage 1 has three substages (Figure 1).

Stage 1.1 – Development of a conceptual framework

Previous work concluded that existing hypoglycaemia-specific PROMs had insufficient evidence supporting their satisfactory reliability, validity and responsiveness for quantifying the impact of hypoglycaemia on QoL in adults with diabetes.[5] As part of the current project, a working, conceptual framework for the impact of hypoglycaemia on HRQoL will be developed. As a starting point, the framework will be informed by domains included in existing condition-specific PROMs and refined following interviews (described below). The conceptual framework will be used to develop a topic guide and deductive coding book to be used in stage 1.2.

Stage 1.2 – Qualitative interviews

Semi-structured interviews will be conducted by two experienced qualitative researchers. Participants will be adults with diabetes who experience hypoglycaemia, identified from an existing research database at a recruiting National Health Service (NHS) site in the United Kingdom (UK). Due to COVID-19 restrictions, interviews will be conducted remotely (either via webchat or telephone) according to participants' preferred date, time and medium. Interviews will be recorded digitally on an encrypted dictaphone, transcribed verbatim and anonymised. After the interview, participants will complete and return a Participant Questionnaire Booklet containing self-reported hypoglycaemia awareness and QoL (as measured by the Hypoglycaemia Awareness Questionnaire Short Form (HypoA-Q SF),[10] the Hypoglycaemia Fear Survey Short Form (HFS-SF),[11] and EQ-5D-5 L[12]). This will allow us to describe the sample in terms of hypoglycaemia awareness and fear experiences. Sociodemographic and clinical data will be obtained from healthcare records.

Interview participants will be identified by a healthcare team at a UK NHS site that specialises in the care and treatment of PLWD. Purposive sampling will be used, based on a predefined sampling framework to ensure representation across age, gender, type of diabetes and duration of diabetes. Recruitment is iterative to ensure that an appropriate breadth of sampling across these characteristics was achieved. Study inclusion and exclusion criteria are shown in Table 1. Sampling continues until sufficient sampling breadth and data saturation are reached, based on an a priori stopping rule of no additional novel themes being coded for three interviews.[13]

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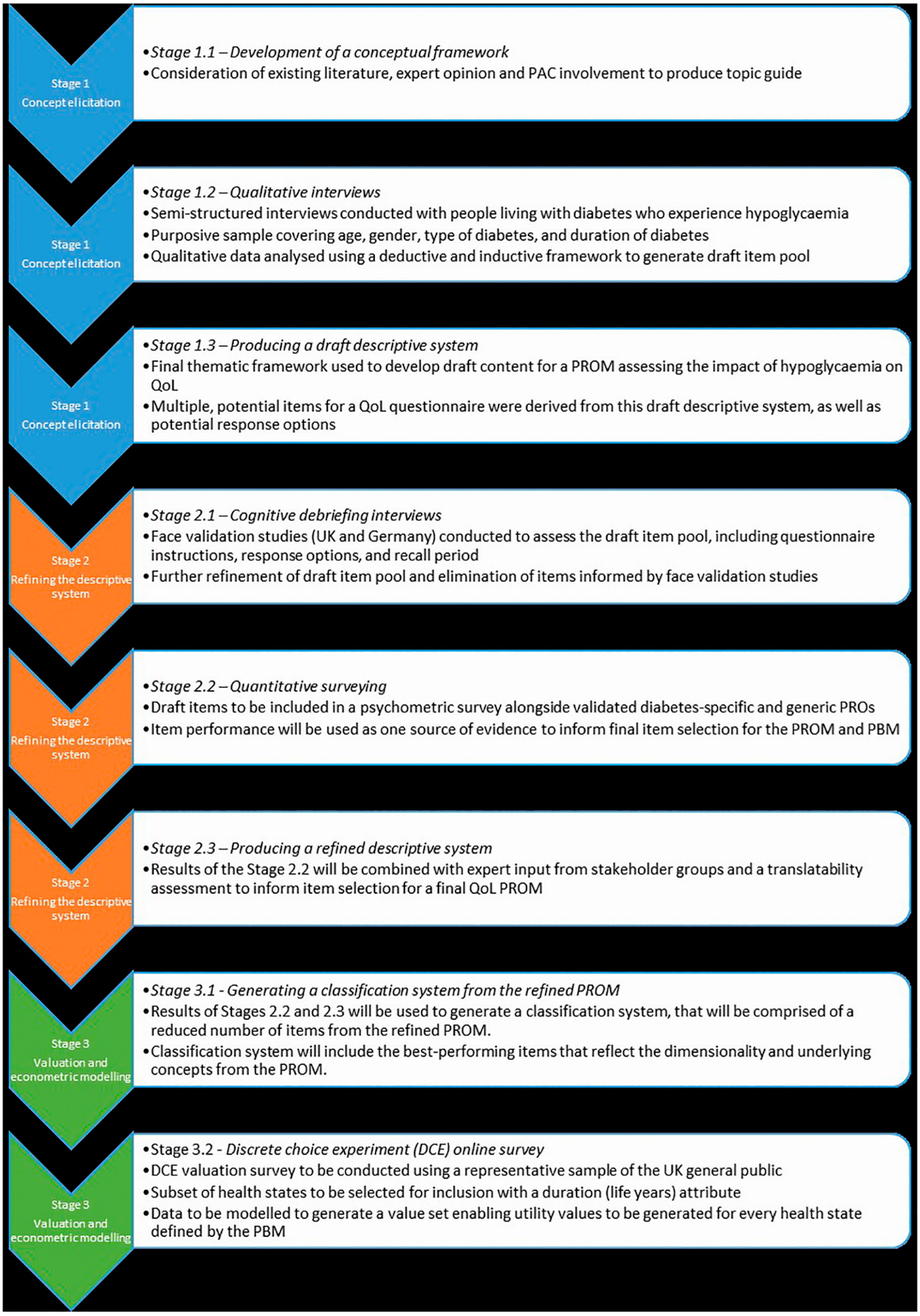

FIGURE 1 Overview of project stages

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TABLE 1 Inclusion and exclusion criteria for the data collection stages of the project

Study stage	Inclusion criteria	Exclusion criteria
Stage 1.2 Qualitative interviews	• Adult (18+ years) • Diagnosis of diabetes • History of hypoglycaemic event(s) in the last 12 months • Fluent in English	• People lacking the capacity to consent
Stage 2.1 Cognitive debriefing interviews	• Adult (18+ years) • Diagnosis of diabetes • History of hypoglycaemic event(s) in the last 12 months • Fluent in English	• People lacking the capacity to consent • Took part in an interview as part of stage 1.2 of the project
Stage 2.2 Quantitative surveying	• Adult (18+ years) • Diagnosis of diabetes • History of hypoglycaemic event(s) in the last 12 months • Able to read in English	• People lacking the capacity to consent
Stage 3.2 Discrete choice experiment online survey	• Adult (18+ years) • Able to read in English	• People lacking the capacity to consent

The transcribed data will be coded alongside data collection using Framework Analysis,[14] following the stages outlined by Gale et al.[15] A concurrent data collection and analysis procedure is advantageous for qualitative research as it facilitates interviewer reflection (e.g., on the quality of the interview and areas for improvement) and monitoring for data saturation. The transcripts will be analysed by two researchers independently, with both researchers analysing their own interviews and 50% of the other researcher's interviews. The initial codebook developed in stage 1.1 will be used and expanded and revised during the analysis. Groups of four transcripts will be coded at any one time before the researchers meet to discuss their coding and any necessary revisions to the working framework. Accordingly, the interviews and analysis will generate knowledge that is both deductive and inductive, as participants will be asked to provide details on any QoL dimensions that they consider important, but which were not included in the original framework or revised interpretations of pre-existing dimensions.

Stage 1.3 – Producing draft PROM content

A final thematic framework, developed after all transcripts are coded, will be used to develop draft content for a PROM assessing the impact of hypoglycaemia on HRQoL, which will be reviewed by the PAC and Scientific Group for comment. Multiple potential items for an HRQoL questionnaire (to be used in stage 2) will be derived, as well as potential response options. The PAC will contribute to item development, providing advice on the wording of items and response options, type of response options and item reduction. Patient advisors will help identify whether any important items are missing. This approach has been applied previously to produce other PROMs in specific health conditions.[16–20]

3.1.2 | Stage 2 – refining the descriptive system

The purpose of stage 2 is to refine the draft PROM content to produce an HRQoL measure. Stage 2 has three substages (Figure 1).

Stage 2.1 – Cognitive debriefing interviews

To assess the face validity of the draft PROM content, cognitive debriefing interviews will be conducted in three iterative waves with a sample of PLWD who experience hypoglycaemia and healthcare professionals (HCPs). Participants will be recruited by the same NHS healthcare team at the same site as stage 1. PLWD will be purposively sampled, to ensure a balance on type and duration of diabetes, age and gender. Participants will be asked about their interpretations of the draft items, response options and any instructions for the HRQoL measure, to help assess whether each element of the draft PROM is relevant, comprehensive (not missing anything important) and comprehensible (understood as intended) to the target population. Due to COVID-19 restrictions, interviews will be offered remotely (i.e., online or by telephone). Cognitive debriefing interviews will be informed by a topic guide based upon the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) criteria of relevance, comprehensiveness and

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comprehensibility,[21] with additional input from the PAC. Interviews will be recorded and transcribed verbatim. Items will be split into three theoretical domains to mirror the framework developed in stage 1: physical, psychological and social components of HRQoL. Due to the number of items developed in stage 1, and taking into consideration response burden, we will adopt an iterative interview process across three waves. Each participant will be asked to review and comment upon up to 40 items only (incorporating one or two domains of HRQoL in their entirety). This methodology and the sample size requirements are based on COSMIN guidance.[22] As this is a European-funded project, the cognitive debriefing interviews will be replicated in Germany to ensure non-UK views are considered, using a similar methodology. Translation of the HypoRESOLVE QoL measure will be based on best practice guidance.[23] Interviews will be conducted in German, transcribed verbatim (in German) and analysed. The results will be translated into English, prior to pooling with UK data.

The qualitative data will be used to assess each element of the draft-HRQoL measure (items, response options, and/or instructions) against the COSMIN content validity criterion for relevance, comprehensiveness and comprehensibility.[21] Supporting qualitative data will be extracted from the transcripts for each criteria by two researchers, who will do this independently for their own cognitive debriefing interviews and 50% of the other researchers' transcripts. Suggestions for refinement made in the transcripts will be extracted by the researchers and used in combination with the ratings to revise the draft questionnaire. The results of this work will be presented to the Advisory Group and PAC for their consideration of the selection of items and exact wording for the item pool.

Stage 2.2 – Quantitative survey for analysis of psychometric properties

The refined set of items will be included in a psychometric survey alongside a selection of existing validated PROs, including two measures of hypoglycaemia awareness (HypoA-Q[10] and Gold score[24]); a generic PBM (EQ-5D-5 L)[12]; a measure of diabetes-specific QoL, the DAWN2 Impact of Diabetes Profile (DIDP)[25]; and a global Visual Analogue Scale (VAS) measure of hypoglycaemia-related QoL ("Thinking about how hypos affect you, how would you rate your quality of life at the moment?" Participants answer using a sliding scale, where 0 is the worst imaginable QoL, and 100 is the best imaginable QoL). Sociodemographic and clinical questions will also be asked in order to demonstrate the representativeness of the sample. In order to address the potential differences in hypoglycaemia-specific HRQoL between adults with type 1 (T1D) diabetes and type 2 (T2D) diabetes, we have set a minimum sample size of $N = 1000$ participants (with an approximate split of T1D $n = 800$; T2D $n = 200$). This will allow analyses to be undertaken if some participant data need to be excluded due to concerns over data quality (see below). Participants will be recruited via existing NHS databases within the UK. The survey will be conducted online using Qualtrics, and paper versions will be available for those who request it. A small subset of participants will be completing the survey again, approximately 1 month after first completion to explore test–retest reliability of the draft items. Based upon an intraclass correlation (ICC) coefficient of 0.5, the level at which a measure is perceived to have a satisfactory agreement,[26] a minimum sample of 22 people is required for test–retest reliability with a power of 80% and an alpha of 0.05.[27] It is expected that the sample achieved will exceed this (e.g., 100+), ensuring more stable estimates.

Prior to analyses, data will be cleaned and assessed for quality. The data will be inspected for multivariate outliers, which can have a disproportionate influence on results using methods described by Leys et al.[28] These outliers will be identified and inspected (examining plausibility of responses) before determining whether data should be excluded from the full analyses. Time to complete the survey will be scrutinised. Anyone who has taken longer than 24 hcor less than the estimated reading time to complete the survey will be excluded from analyses. Responses for the Hypo-RESOLVE QoL will be examined for straight-lining (this should not be plausible given that some items are reversed). For completeness, results will be modelled both with and without exclusions.

Analyses will be conducted in R in an iterative manner, as described by Dima.[29] Descriptive analysis will be used to summarise the data, including responses to the draft PROM items, as well as exploring the distribution of responses for evidence of items with low variation across response options and/or ceiling/floor effects. These will be followed by psychometric and item response theory (IRT) analyses of the draft PROM to obtain the maximum amount of relevant information on item and scale performance to inform item selection. This will include a tripartite confirmatory factor analysis (CFA), based on a theoretical model of physical, psychological and social factors, with follow-up exploratory factor analyses (EFAs) if necessary to help identify a parsimonious factor structure during item selection. An appropriate polytomous IRT model will be used, and analyses will include tests of item fit, information function, threshold ordering and differential item functioning (e.g. between genders and people with T1 and T2 diabetes).

In addition to psychometric investigations of the draft PROM, correlations will be estimated between the draft items and (a) frequency of hypoglycaemic episodes; (b) the

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global measure of hypoglycaemia-related QoL, to aid with item selection. Following the item selection procedure, the resulting PROM (and associated subscales) will be scored and correlations will be estimated between the new Hypo-RESOLVE QoL and all study variables, including the DIDP and EQ-5D-5 L. Initial exploratory comparisons will then be made by looking at two aspects. First, construct validity – we expect scores on the Hypo-RESOLVE QoL to correlate significantly (at >0.3) with scores on the DIDP and EQ-5D-5 L, with the coefficient to be larger for the former (diabetes-specific) than the latter (generic). We expect scores on the Hypo-RESOLVE QoL to have a stronger correlation with the global hypoglycaemia-specific QoL (VAS) measure than with the DIDP or the EQ-5D-5L. Second, explore known-group validity investigating how the number of hypoglycaemic episodes affects QoL (as measured by the Hypo-RESOLVE QoL and other PROMs). Given that these data are involved in item selection of the PROM, these analyses are wholly exploratory and will be reported for information only, with the caveat that additional confirmatory validation of the Hypo-RESOLVE QoL, including sensitivity to change in HRQoL, is needed in future work.

Stage 2.3 – Producing a refined PROM

The results of stage 2.2 will be combined with expert input from the PAC, Scientific Group and Advisory Group, and a translatability assessment (an assessment of how well draft content translates into different languages) to inform item selection for a final HRQoL PROM. These decisions will be made in consensus by the research team. This approach follows that of other instruments.[18–20,30]

3.1.3 | Stage 3 – Valuation and econometric modelling

A PBM consists of (a) a health state classification system that defines the health-related QoL of patients; and (b) a scoring system based on preferences that are used to generate utility values for every state defined by the classification system. Development of the PBM will be undertaken in two stages.

Stage 3.1 Generating a classification system from the refined PROM

The results of stages 2.2 and 2.3 will be used to generate a classification system that will consist of a reduced number of items from the refined PROM. The classification system will include the best-performing items that reflect the dimensionality and underlying concepts from the PROM. A parsimonious number of items is required for valuation for participants to be able to meaningfully consider all items simultaneously. The minimum number of items is selected (usually only one item) per concept.

Stage 3.2 Discrete choice experiment online survey

A discrete choice experiment (DCE) will be designed taking into account any unidimensional components within the classification system. DCEs are used in health economics for the purposes of eliciting preferences for different states of health or QoL. Each state will have an additional duration attribute of life remaining in years. An online DCE survey will be conducted with a sample of N = 1000 members of the UK general population representative for age and gender. Participants are selected from the general population, rather than the population of adults living with diabetes, in line with NICE recommendations for the generation of utility values to inform economic evaluation (NICE, 2022).[7] Participants will be recruited by a market research company using existing panels where individuals have agreed to complete surveys. Each survey participant will complete 10 DCE choices, where they are asked which of two states they prefer. The results will be modelled using regression analysis, to generate utilities for every state defined by the classification system.[31] This will enable a utility value to be generated each time the PROM is completed, where this utility value is on a 1–0 scale where 1 = full health, 0 = dead, and values below 0 reflect that the health state is considered to be worse than dead.

4 | STRENGTHS AND LIMITATIONS

This research follows recognised best practice guidelines for the development of PROMs.[32–34] The international multidisciplinary Scientific Group and PAC enable us to incorporate various perspectives, to ensure an instrument that will be useful in both research and clinical practice. The final instrument will be suitable for use in English in the UK. Further work will be required to determine whether any cultural adaptations of the English version of the instrument are needed. During the development of the instrument, initial psychometric testing will be conducted. However, further validation will be required to assess the full psychometric properties of the final instrument.

5 | DISCUSSION

Existing hypoglycaemia-specific PROMs have been shown to lack evidence of validity and reliability for the specific purpose of assessing the impact of hypoglycaemia on quality of life.[5] Furthermore, no hypoglycaemia-specific PBMs exist that can be used to estimate QALYs

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for use in the economic evaluation of healthcare interventions (including education, treatment and technologies) designed for preventing or managing hypoglycaemia. The mixed-methods project presented in this protocol is designed to generate a novel PROM and PBM, following best practice principles and methods, which will fill a critical gap in this field of research. The primary outcome will be a PROM and associated PBM suitable to assess the impact of hypoglycaemia on HRQoL, and an associated value set for use in cost-effectiveness evaluations.

Ethical considerations

The work will be conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research. Stages 1 and 2 of the study have received Health Research Authority approval and a favourable ethical opinion from the Office for Research Ethics Committee Northern Ireland (ORECNI) (REC reference: 20/NI/0048).

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